Original Article

Risk Factors, Clinical Profile, and Management Outcome of Patients with Isolated Subsegmental Pulmonary Embolism: A Single-Center Experience from North India

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Abstract

Background and Objective: The clinical profile of patients with isolated subsegmental pulmonary embolism (SSPE) remains understudied and underreported. To describe the clinical particulars of patients with SSPE, we aimed to compare clinical signs and symptoms, risk factors, lab parameters, and short-term mortality between patients with isolated SSPE and those with proximal pulmonary embolism (PE). **Materials and Methods:** We prospectively studied all patients with objectively confirmed PE over 4 years. Depending on the location of the most proximal pulmonary artery in which emboli were detected, patients were divided into two groups: (a) isolated SSPE and (b) proximal PE. Different clinical and laboratory parameters were compared between the two groups. **Results:** One hundred and fifty patients were enrolled during the 4-year study. Twenty-three (15.3%) patients were diagnosed with isolated SSPE. Compared to proximal PE, patients with SSPE are younger, are more likely to have active malignancy, less likely to have dyspnea, and more likely to have chest pain, are hemodynamically stable with a lesser prevalence of hypoxemia and hypocapnia. Patients with isolated SSPE have shorter hospital stays and lower 30-day mortality compared to proximal PE. **Conclusion:** Patients with isolated SSPE have a mild clinical presentation, lesser laboratory abnormalities, and a favorable short-term outcome compared to patients with proximal PE.

Keywords: Pulmonary embolism, pulmonary embolism severity index, subsegmental pulmonary embolism, venous thromboembolism

Introduction

Acute pulmonary thromboembolism (PTE) is a relatively common and potentially fatal disease with an annual incidence rate of about 104–183 per 100,000 person-years and 30-day mortality of around 10%.[1,2] With the introduction of multidetector-row computed tomography (MDCT) in the diagnostic evaluation of patients with suspected pulmonary embolism (PE), PTE diagnosis has significantly increased. The high sensitivity of MDCT allows visualization of filling defects in arteries as small as 2–3 mm in diameter, termed as subsegmental pulmonary arteries.[3,4]

Despite the increasing incidence of isolated subsegmental pulmonary embolism (SSPE), the clinical relevance of its diagnosis is still debatable. Many cases of SSPE are believed to represent false-positive results (e.g., artifacts) rather than true PTE. Some authors also believe that SSPE may represent a normal finding as lungs act as natural filters to protect systemic circulation. Moreover, whether SSPE represents a more benign clinical condition or if mortality and risk factors truly mirror proximal PTE is unclear.[5,6]

To describe the clinical profile of patients with SSPE, we compared clinical signs and symptoms, PTE risk factors, lab parameters, and short-term mortality between patients with isolated SSPE and those with proximal PTE.

Materials and Methods

It was a hospital-based observational prospective study conducted in north India at a leading tertiary care institute.

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An approval to conduct the study was obtained from the hospital's Institutional Review Board. However, this study did not involve any diagnostic or therapeutic maneuver outside of the routine evaluation of these patients and did not entail any extra costs to them.

The study began in August 2015, and the recruitment of patients concluded in September 2019. Patients admitted to the hospital with an initial diagnosis of PTE were included in the study. Only those patients who had a diagnosis of PTE confirmed by visualization of embolus by computed tomography (CT) pulmonary angiography were included in the study. Patients with a previous history of PTE irrespective of their current treatment status were excluded from this study.

For all enrolled patients, we prospectively collected information about baseline demographics (age and sex), venous thromboembolism (VTE) risk factors (immobilization for at least 3 days, major surgery in the preceding 3 months, active malignancy, previous stroke, chronic lung disease, chronic heart failure, and pregnancy or postpartum period), symptoms of PTE (dyspnea, chest pain, cough, hemoptysis, palpitations, and altered mental status), clinical signs of PE (tachycardia with heart rate of >100, tachypnea with respiratory rate of >24, hypotension with systolic blood pressure of <90 mmHg, lower extremity edema, and fever), common laboratory findings (anemia with hemoglobin <10 g/dl, leukocytosis >11,000/ul, thrombocytopenia <1.5lac/ul, hypoxemia with saturation of <90% at ambient temperature, hypocapnia with pco2 <35 mm Hg, respiratory alkalosis, D-dimer levels, and elevated troponins detected by rapid card tests), and electrocardiogram (ECG) and echocardiographic findings of PTE (sinus tachycardia, S1Q3T3 pattern, RBBB, right axis deviation, and right ventricular dysfunction). A Pulmonary Embolism Severity Index (PESI) score was calculated for all enrolled patients. The outcome was calculated in terms of prolonged hospital stay (hospital stay of ≥10 days), treatment-related bleeding complications, and all-cause in-hospital and 30-day mortality.

Depending on the location of the most proximal pulmonary artery in which emboli were detected by an on-site radiologist, patients were divided into two groups: (a) isolated SSPE in which emboli were detected only in subsegmental arteries and (b) proximal PTE in which emboli were seen in proximally located pulmonary arteries. To study the characteristics of patients with isolated SSPE patients, clinical features, risk factors, and hospital outcome was compared with patients with proximal PTE.

Statistical analysis

The recorded data were compiled and entered in a spreadsheet (Microsoft Excel) and then exported to the data editor of SPSS Version 22.0 (IBM, Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were reported as frequencies and percentages. The student's independent *t*-test was employed for comparing continuous variables between the two cohorts. Chi-square test (corrected, uncorrected, and Mantel–Haenszel) and exact tests (Fisher and mid-p exact), whichever appropriate, were applied for comparing categorical variables. A $P < 0.05$ was considered statistically significant. All *P* were two-tailed.

Results

A total of 150 PE patients were enrolled during the 4-year study. 23 (15.3%) patients were diagnosed with isolated SSPE. Compared to proximal PE, patients with SSPE were younger, with a mean age of 45.3 years (SD = 15.37). Among the VTE risk factors, patients with SSPE were more likely to have active malignancy (30.4% vs. 12.5%, $P = 0.042$). The rest of the thromboembolic risk factors showed no significant differences between the two groups [Table 1].

Patients with isolated SSPE were less likely to have dyspnea (73.9% vs. 97.6%, $P < 0.001$) and more likely to have chest pain (60.8% vs. 33.8%, $P = 0.018$) as compared to proximal PE. Other symptoms were comparable between the two groups. Patients with SSPE were hemodynamically stable, with none having hypotension. Furthermore, patients in SSPE group had lesser prevalence of tachycardia (73.9% vs. 90.6%, $P = 0.024$) and tachypnea (60.9% vs. 85.0%, $P = 0.006$) [Table 2].

Patients with isolated SSPE exhibited more favorable lab parameters than proximal PE and had a lower prevalence of leukocytosis, hypoxemia, hypocapnia, respiratory alkalosis, and elevated troponins. These patients' mean D-dimer levels were also low compared to those with proximal PE [Table 3]. SSPE patients were also more likely to have normal echocardiography. However, ECG findings were comparable between the two groups [Table 3].

Patients with isolated SSPE were less likely to have the severe disease than proximal PE, as indicated by PESI class. Only 2 (8.7%) patients with SSPE belonged to PESI class V as compared to 42 (33.1%) patients with proximal PE [Figure 1].

All the patients received anticoagulation. Clinical outcomes in all-cause in-hospital mortality and treatment-related bleeding complication did not differ between the two groups. However, isolated SSPE were less likely to have prolonged hospital stays and had less 30-day mortality than proximal PE [Table 4].

Discussion

This study has provided important insights into the clinical profile of patients with isolated SSPE. The rate of SSPE diagnosis among objectively confirmed PE patients has increased from around 4.7% in the era of single-detector computed tomography pulmonary angiography to 15% in the era of MDCT.[7,8] The increased sensitivity of MDCT in detecting filling defects up to the subsegmental level has led to this substantial increase in SSPE incidence.[7] In our study, the prevalence of isolated SSPE was 15.3%, similar to that reported in the literature using MDCT as a diagnostic modality.[7-10]

Table 1: Demographic characteristics and risk factors of patients with isolated subsegmental pulmonary embolism versus proximal pulmonary embolism

Variable	SSPE (n=23)		Proximal PE (n=127)		P
	n/mean	Percentage/SD	n/mean	Percentage/SD	
Demographics					
Age (years)	45.3	15.4	53.5	15.7	0.022*
Male (sex)	14	60.9	52	40.9	0.077
Risk factors					
Immobilization	7	30.4	43	33.8	0.768
Malignancy	7	30.4	16	12.5	0.042*
Surgery within the last three months	4	17.3	15	11.8	0.467
Chronic lung disease	3	13.0	31	24.4	0.241
Heart failure	3	13.0	14	11.0	0.752
Pregnancy/postpartum period	2	8.6	3	2.36	0.194
Previous stroke	1	4.3	10	7.8	0.622

*Statistically significant difference (P<0.05). SD: Standard deviation, PE: Pulmonary embolism, SSPE: Isolated subsegmental PE

Table 2: Clinical signs and symptoms of patients with isolated subsegmental pulmonary embolism versus proximal pulmonary embolism

Variable	SSPE, n (%)	Proximal PE, n (%)	P
Symptoms			
Dyspnea	17 (73.9)	124 (97.6)	<0.001*
Pleuritic chest pain	14 (60.8)	43 (33.8)	0.018*
Cough	6 (26.1)	45 (35.4)	0.384
Palpitations	1 (4.3)	23 (18.1)	0.098
Decreased level of consciousness	2 (8.7)	20 (15.7)	0.379
Hemoptysis	5 (21.7)	10 (7.8)	0.070
Signs			
Tachycardia	17 (73.9)	115 (90.6)	0.024*
Tachypnea	14 (60.9)	108 (85.0)	0.006*
Lower extremity edema	11 (47.8)	83 (65.3)	0.122
Hypotension	0	50 (39.3)	<0.001*
Fever	2 (8.7)	16 (12.6)	0.596

*Statistically significant difference (P<0.05). PE: PE: Pulmonary embolism, SSPE: Subsegmental pulmonary embolism

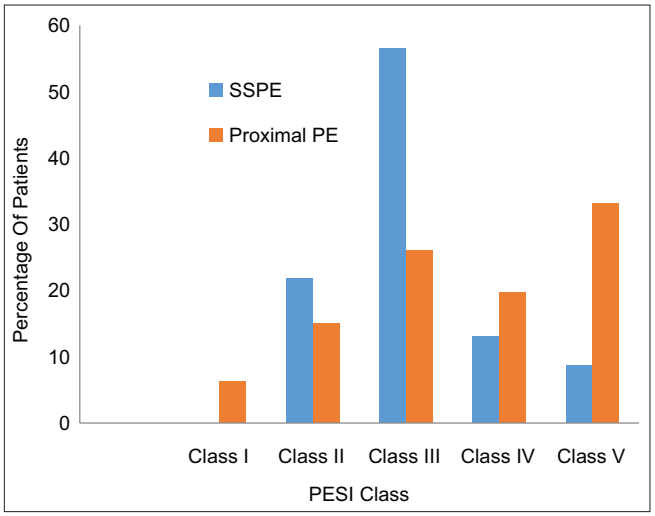

Figure 1: Pulmonary embolism severity index class of subsegmental and proximal pulmonary embolism

Patients with isolated SSPE in our study were younger than patients with proximal PE, consistent with the results of previous studies.[11] This difference could be attributed to defective fibrinolysis and changes in vascular endothelium associated with aging, resulting in bigger embolus size with subsequent lodgment in more proximal arteries.[12]

Except for the higher prevalence of active malignancy in patients with isolated SSPE, there was no significant difference in the prevalence of other thromboembolic risk factors between patients with isolated SSPE and patients with proximal PE. This indicates that the same underlying pathophysiological mechanism is responsible for proximal and peripheral emboli. Increasing the use of thoracic CT in patients with malignancy for the staging process may be responsible for an increased rate of detection of asymptomatic SSPE in these patients. Similar results were reported by Stoller *et al*. in their study.[13]

Isolated SSPE is clinically more benign than proximal PE, as demonstrated by our study also. Although dyspnea was the most common presenting symptom in both SSPE and PE, it was more common in patients with proximal PE. On the other hand, pleuritic chest pain was more commonly found in patients with SSPE. Furthermore, patients with SSPE were hemodynamically stable and had a lesser prevalence of tachypnea and tachycardia than patients with proximal PE. These results are in concordance with a previously published study by Cha *et al*.[14]

Patients with SSPE had a more favorable laboratory profile also. Our study showed that patients with subsegmental PE had a lesser prevalence of elevated leukocyte count, hypoxemia, hypocapnia, and respiratory alkalosis. These results are consistent with Cha *et al*. and Alonso Martinez *et al*., wherein patients with proximal PE were found to have significantly more chances of hypoxemia and hypocapnia.[14,15] Patients with isolated SSPE were also found to have significantly lower

Table 3: Common laboratory findings in patients with isolated subsegmental pulmonary embolism versus proximal pulmonary embolism

Parameter	SSPE		Proximal PE		*P*
	n/mean	Percentage/SD	*n*/mean	Percentage/SD	
Hemoglobin <10 g/dL	6	26.1	27	21.3	0.607
TLC >11,000/ul	5	21.7	64	50.4	0.011*
PLT <1.5 lac/ul	8	34.7	55	43.3	0.460
Hypoxemia (pO_2 <60 mmHg)	8	34.7	87	68.5	0.003*
Hypocapnia (pCO_2 <35 mmHg)	5	21.7	58	45.6	0.032*
Respiratory alkalosis (pH >7.45 and pCO_2 <35)	01	4.3	31	24.4	0.023*
D Dimer	1701.8	958.5	2264.5	1038.9	0.016*
Elevated troponins	1	4.3	45	35.4	0.002*
Normal ECG	4	17.3	14	11.0	0.403
Sinus tachycardia	17	73.9	84	66.1	0.465
S1Q3T3	2	8.7	24	18.9	0.234
RAD	0	0.0	5	3.9	0.598
RBBB	0	0.0	10	7.9	0.226
Normal echo	18	78.2	36	28.3	<0.001*
RV dysfunction	03	13.0	65	51.1	<0.001*

*Statistically significant difference (*P*<0.05). ECG: Electrocardiogram, RBBB: Right bundle branch block, RAD: Right axis deviation, RV: Right ventricular, PE: Pulmonary embolism, SSPE: Subsegmental PE, SD: Standard deviation, TLC: Total leukocyte count, PLT: Platelet count test

Table 4: Clinical outcome of patients with isolated isolated subsegmental pulmonary embolism versus proximal pulmonary embolism

Variable	SSPE, *n* (%)	Proximal PE, *n* (%)	*P*
Prolonged hospital stay (i.e., ≥10 days)	7 (30.4)	76 (59.8)	0.012*
Treatment related bleeding complications	1 (4.3)	18 (14.2)	0.309
In-hospital mortality	0	14 (11.0)	0.086
30-days mortality	1 (4.3)	27 (21.2)	0.047*

*Statistically significant difference (*P*<0.05). PE: Pulmonary embolism, SSPE: Subsegmental PE

D-dimer levels than patients with proximal PE, which could be attributed to a lesser burden of thrombosis in these patients.

Our study showed that patients with emboli limited to subsegmental arteries were more likely to have normal echocardiography and less likely to have elevated troponin levels than patients with emboli in more proximal pulmonary arteries. These findings are in concordance with previously published studies.[15,16]

Although the localization of pulmonary emboli within the pulmonary arterial tree was not considered a matter of severity, our study showed that patients with isolated SSPE had a lesser PESI risk class than patients with proximal PE. Stoller *et al*. did not find a statistically significant difference between the PESI class of patients with isolated SSPE and proximal PE.[13] Two reasons could explain this deviation: (1) patients with SSPE were much younger than previously published literature and (2) patients with subsegmental PE had a lesser prevalence of hypoxemia, hypotension, tachypnea, and tachycardia.[11-14]

Patients with PE are often admitted to the hospital for initial management, and PE-related hospitalization is a substantial burden on health care. The present study revealed that patients with isolated SSPE were less likely to have prolonged hospital stays, thus reducing hospitalization costs. Regarding clinical outcomes, regarding bleeding complications, and all-cause in-hospital mortality, patients with SSPE appeared to mimic those with proximal PE. 30-day mortality was, however, more in proximal PE. These results are consistent with several studies supporting that emboli affecting the small pulmonary arteries carry a better prognosis.[14,15]

Limitations

Although this study has provided important insights into the clinical features of patients with isolated SSPE, especially in the Indian population, our study has few limitations. First, the sample size was small, and the patients were taken from a single center. Second, the diagnosis of SSPE was made by on-site radiologists and was not independently reviewed. Finally, the number of outcome events was very small, and hence results cannot be generalized.

Conclusion

To conclude, SSPE may be viewed as a clinically indolent form of PE with a favorable laboratory profile. These patients have shorter hospital stays and have a good clinical course with lower 30-day mortality than patients with proximal PE.

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Conflicts of interest
There are no conflicts of interest.

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